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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/805,881	03/22/2004	Ibert C. Wells	800812-0005	9725

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EXAMINER	
SZPERKA, MICHAEL EDWARD	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 08/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/805,881	WELLS, IBERT C.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6,19 and 31-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-6, 19, and 31-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response and amendments received June 16, 2006 are acknowledged.

Claims 2, 7-18, and 20-30 have been canceled.

Claims 1, 3, 5, 19, 31, 32, 34, 36, and 37 have been amended.

Claims 1, 3-6, 19, and 31-40 are pending in the instant application.

Declaration A of Ibert C. Wells under 37 CFR 1.132 received June 16, 2006 is acknowledged and will be discussed in conjunction with the rejections of record where appropriate.

Claim Objections

2. The objection to claims 1, 3, 19, 31, 32, 36, and 37 for grammatical correctness due to the lack of a recited article in conjunction with the phrase "amino acid sequence set forth in SEQ ID NO:x" has been withdrawn due to applicant's claim amendments received June 16, 2006 which insert articles where appropriate.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

4. Claims 1, 3-6, 19 and 31-40 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention for the reasons of record.

The office action mailed December 16, 2005 states that:

Applicant's arguments filed October 11, 2005 have been fully considered but they are not fully persuasive. Applicant argues that the specification does provide evidence for a correlation between the level of Peptides (term used by applicant to collectively refer to the peptides consisting of SEQ ID NOs:1, 2, and 4) and the magnesium binding defect (MgBD). Applicant further argues that the specification teaches in example 4 that women diagnosed with preeclampsia also have MgBD as determined by measuring Mg bound to erythrocyte membranes. Applicant then argues the conclusion that since Peptides correlate with MgBD, and MgBD correlates with preeclampsia, then Peptides must correlate with preeclampsia.

This is not convincing for the reasons of record, namely that applicant has not shown a direct link between the direction of Peptides and the detection of preeclampsia. Applicant is correct in the statement that the specification teaches that the administration of Peptides to rats *in vivo* corrected hypertension and MgBD, and that *in vitro* incubation of Peptides with human erythrocytes increased Mg binding to the plasma membrane (see particularly paragraph 47, Examples 2, 3 and 7). However, support for applicant's statement in the middle of the first paragraph of page 10 of the reply indicating that the measured plasma level of Peptides was decreased in a rat model of MgBD as compared to the measured value in controls could not be located in Example 2 or paragraph 47, and applicant is invited to clearly point out where support for this statement can be found. As such, it while administration of peptides may reverse MgBD, it is not clear that detection of lower than normal levels of Peptides is causative of MgBD or is predictive of the presence of MgBD. In the absence of such evidence, applicant's chain of associative reasoning fails, and one cannot reasonably conclude that the detection of Peptides correlates with preeclampsia. Further, as was noted in the rejection of record, neither the detection of Peptides nor the detection of MgBD is an art recognized method for diagnosing preeclampsia as taught by Merck.

Applicant also argues that the teachings of Page et al. discussed in the rejection of record are not relevant because they address the full length polypeptide of NKB and not the breakdown products of NKB (the genus of which reasonable includes the polypeptides consisting of SEQ ID NO:2 and 4). The rejection or record acknowledges applicant's point, but it is not clear to the examiner how if the concentration of a precursor sequence increases (i.e. NKB), the concentration of its breakdown products (i.e. SEQ ID NO:2, 4) decreases, and applicant is still invited to address this issue.

The instant claims also indicate that the recited method detect a predisposition in an individual that places them at risk for developing preeclampsia. Applicant's arguments concerning this issue are not persuasive. First, applicant's amendment has removed references to pregnancy in an attempt to clarify the intended patient population. However, this amendment appears to remove the indication that the claimed method be performed on female patients, and since males cannot have preeclampsia the instant method claims do not appear to be enabled for about 50% of the human population. Second, applicant argues that the examiner is unreasonable in the statement that predisposition indicates that something (in the instant case, preeclampsia) is more likely than not to happen at a future date. Applicant has provided dictionary references that define predisposition as "tendency, inclination or susceptibility" and "a condition of special susceptibility, as to a disease." In order for a tendency, inclination, or susceptibility to be observed in a patient population that item must occur more often than what would be expected to occur due to random chance in said patient population. In the instant case, this would mean that detection of Peptides in a woman means that the woman is more likely to develop preeclampsia than what would be predicted to happen due to random chance. If an outcome is more likely than not to occur, it is occurring at a frequency greater than that which would be expected by random chance. As such, the examiner's statement in the rejection of record is in accord with the definitions entered by applicant and with the connotations of what this term means to a skilled artisan. Further, if variables are truly correlated, (such as Peptide level and risk of preeclampsia) then observation of one variable would make it more likely than not that the other variable will be detected. As was stated in the rejection of record, the specification does not provide evidence that measuring Peptides in a female patient has predictive power in selecting those individuals that will develop preeclampsia, and as such no predisposition to developing preeclampsia can be detected by performing applicant's claimed methods. For all of the above discussed reasons the rejection is maintained.

Applicant's arguments filed June 16, 2006 have been fully considered but they are not persuasive. Applicant repeats arguments of record, namely that "To summarize, the instant specification provides evidence that a significantly lower than normal level of Peptides correlates with the presence of the magnesium binding defect, and, together with the teachings of the specification that preeclampsia is associated with the

magnesium binding defect, the specification enables one of skill in the relevant art to make and use the claimed invention." (bottom of page 10 of the reply received June 16, 2006).

This argument is not persuasive for the reasons discussed in the prior office action. As previously stated, the specification provides evidence that administering Peptides reverses the magnesium binding defect (Examples 2, 3, and 7) and indicates that the magnesium binding defect is associated with preeclampsia (Example 4). None of these observations is direct evidence that a skilled artisan can measure Peptides to detect the magnesium binding defect or that the lack of Peptides causes or is correlated with the presence of the magnesium binding defect.

Declaration A of Ibert C. Wells provides a theory of the inventor concerning how Peptides are involved in the magnesium binding defect, but does not provide data demonstrating that lower than normal levels of Peptides are detected in samples that have the magnesium binding defect. As such, the declaration is not persuasive that the detection of Peptides is correlated with the magnesium binding defect.

Further, applicant has attempted to clarify the statement made in the reply received October 11, 2005. Specifically, the statement in the previous reply was that the measured plasma level of Peptides was decreased in rats that have the magnesium binding defect as compared to normal control animals, and applicant pointed to lines of the specification and the prior art to support this statement. The office action mailed December 16, 2005 indicated that the examiner could not find support for applicant's statement in the places indicated by applicant, and the examiner asked applicant to point out where support for such a statement is located.

In response, applicant has provided a synopsis of what was known in the prior art. However, the prior art does not teach the measurement or detection of Peptides, and therefore the prior art cannot be said to teach that detection of Peptides is correlated with the magnesium binding defect. The correlation between the detection of Peptides and the magnesium binding defect is critical to the claimed invention, yet this correlation has not been demonstrated in the prior art or the instant specification.

Therefore, the rejection is maintained.

5. Claims 19 and 31-35 stand rejected and claim 5 as amended June 16, 2006 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of measuring peptides consisting of SEQ ID NO:1 or SEQ ID NO:4, does not reasonably provide enablement for methods of measuring peptides consisting of SEQ ID NO:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims for the reasons or record.

The office action mailed December 16, 2005 states that:

> Applicant's arguments filed October 11, 2005 have been fully considered but they are not persuasive. Applicant has argued that only routine experimentation would be required to generate an antibody that binds to a peptide consisting of SEQ ID NO:2. SEQ ID NO:2 is a tetrapeptide that is completely contained within the larger pentapeptide of SEQ ID NO:1. SEQ ID NO:4 is degenerate pentapeptide that contains SEQ ID NO:1 and the sequence FVGLM. Applicant argues that it was recognized in the art that epitopes are often comprised of only 4 or 5 amino acids, and that only routine screening would be required to find an antibody that had the ability to bind to a tetrapeptide consisting of SEQ ID NO:2. The examiner agrees that antibodies may be able to bind a linear peptide epitope that consists only of four amino acids, and as such tetrapeptides can be *antigenic*. However, Harlow et al. teach that the smallest synthetic peptide that will consistently elicit antibody responses (and hence is *immunogenic*) is 6 amino acids in length, with approximately 10 amino acids being preferred as the lower limit for the production of antibodies (see Harlow et al., Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory, 1988, cited by applicant on page 15, paragraph 46 of the instant specification, specifically Chapter 5, page 76). As such, the generation of an antibody that binds an epitope of 4 amino acids is not considered a routine procedure that is generally performed in the art. As has been stated in the rejections of record, Couraud et al. (J Neurochem, 1987, 49:1708-1719, of record, see entire document) performed standard, art recognized procedures described by Harlow et al. in generating their antibodies. Specifically, they teach polyclonal and monoclonal antibodies that were generated using the 11 amino acid neuropeptide substance P (SP), and they mapped the binding of these reagents to smaller polypeptide sequences. Their data indicated that while antibodies that bind a pentapeptide consisting of SEQ ID NO:1 were readily observed (the polyclonal serum and 5 out of 5 distinct monoclonal antibodies), no reactivity was observed to the tetrapeptide consisting of SEQ ID NO:2. The lack of binding in the polyclonal serum is particularly noteworthy, since it indicates that antibodies with the requisite binding specificity are not readily generated.
>
> Given that the application does not disclose a working example that uses antibodies that bind the polypeptide sequence of SEQ ID NO:2, that antibodies that bind some but not all SP fragments (one of which includes the peptide of SEQ ID NO:1) as taught by Couraud et al. were generated using standard, art recognized techniques, that while it is known that antibodies can bind small linear peptides, such as a peptide consisting of 4 amino acids, it is not routine to generate antibodies using such small sequences as an immunogen as taught by Harlow et al., and since the specification does not indicate that anything other than standard art recognized procedures are required to make an antibody that binds a tetrapeptide consisting of SEQ ID NO:2, it does not appear that a skilled artisan would be able to make and use the full breadth of applicant's claimed invention, especially in the absence of evidence to the contrary. Therefore the rejection of record is maintained.

Applicant's arguments filed June 16, 2006 have been fully considered but they are not persuasive. Applicant bases many of the arguments on declaration B of Ibert C.

Wells. No such declaration can be found in the instant application, and as such the arguments are not persuasive.

Applicant also repeats arguments of record that the failure of Couraud et al. to generate antibodies of the recited antigen binding specificity does not demonstrate lack of enablement for the claimed invention.

The specification does not comprise a working example of antibodies of the desired binding activity, but it does teach standard, well-known prior art techniques for producing antibodies. Couraud et al. used standard, well known prior art techniques in generating their antibodies, none of which comprised the desired binding specificity. The specification does not teach additional techniques other than standard, well known prior art techniques and as such a skilled artisan would not reasonably be able to make and use the full breadth of applicant's claimed method. Note that claim 5 has been amended to recite the new limitation of SEQ ID NO:2, and as such the claim is properly joined to this rejection.

Applicant also argues that detection of the recited peptides by antibodies is not a limitation of independent claims 19 and 31. Starting at paragraph 57, the specification teaches the detection of peptide levels in blood serum or plasma. This section discusses the use of antibody based immunochemical procedures, and the specification does not appear to provide guidance or direction concerning how to perform non-antibody based detection methodologies. Claims are to be given their broadest reasonable interpretation commensurate in scope with the disclosure of the specification. Given that the specification does not disclose or give specific guidance or direction concerning the use of non-antibody based methods, a rejection based upon the use of antibodies in such a method is reasonable. Additionally, a dependent claim further limits an independent claim, and as such a proper rejection of a dependent claim must also apply to the broader claim from which it depends.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. The rejection of claims 5 and 34 under 35 U.S.C. 112, second paragraph, has been withdrawn in view of applicant's claim amendments received June 16, 2006. Specifically the claims now recite the sequence to which a crosssreactive antibody binds.

8. No claims are allowable.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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August 10, 2006

8/19/06

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PRIMARY EXAMINER